MJFF MISSION AND APPROACH
Our Mission

To accelerate the development of improved therapies, and ultimately a cure, for people living with Parkinson’s disease today.

Vital Stats

» Founded in 2000 by actor Michael J. Fox
» Public charity
» 58,000 donors in 2013 (individuals, corporations, nonprofits)
» No chapters: team of 90 based in NYC
» 1,500 grassroots fundraisers reaching 100,000 supporters worldwide in 2013

» $450 million in research funded to date
  – $71 million in 2013 alone
» 1,300 projects funded to date
» 450 active grants in current portfolio
» 30% of funded project are outside of the U.S.
» Fund academics, biotechs and pharma
MJFF was founded by a person with Parkinson’s disease.

Assessing all potential projects through a patient-focused lens, everything we do is driven by the many unmet medical needs of Parkinson’s patients today.
MJFF has no endowment and deploys 89¢ of every dollar spent to research.
Our ever-evolving funding strategy allows us to invest where our dollars will have the greatest impact and potential to change patients’ lives.
Our team of experts identifies and manages the most compelling science in PD research, while our strategic project managers apply business principles to ensure efficiency and speed progress.
VENTURE PHILANTHROPY DEFINES OUR ROLE IN DRUG DEVELOPMENT

MJFF is focused on moving projects through the pipeline to ultimately de-risk the PD field for larger funders by

» Addressing field-wide challenges
» Aligning the field around priorities
» Investing in riskier projects
» Providing non-dilutive funding
We drive promising therapeutic targets while also investing to make PD drug development faster, cheaper, and more attractive.
Our goal is to advance as many therapeutics as possible into clinical trials.
RESEARCH UPDATE
WHAT IS PARKINSON’S DISEASE?

The Symptoms

» “Motor” Symptoms
  – Slow movement ("bradykinesia")
  – Rigidity
  – Resting tremor
  – Postural instability

» “Non-Motor” Symptoms
  – Cognitive impairment and mood problems
  – Sleep problems
  – Reduced smell ability
  – Constipation
  – Swallowing and speech impairment

Current treatments for PD help reduce the motor symptoms but do not slow or stop the progression of the disease and many ‘non-motor’ symptoms remain poorly managed
MJFF employs various mechanisms and a customized approach to carry out our strategy across all states of PD progression.
Scientists think that the cause of Parkinson’s falls on a continuum, with some due more to genetics, others from environmental factors and many a mix of the two.
ENVIRONMENTAL FACTORS: MPTP

MPTP has become a crucial preclinical model in which to test potential PD therapeutics.
ENVIRONMENTAL FACTORS: PESTICIDES

- Pesticides
- Weed killers
- Solvents
- Farming

In 2000, rotenone shown to cause PD symptoms in preclinical models
GENETIC FACTORS: WHY STUDY RARE MUTATIONS?

• Most cases of Alzheimer’s are not hereditary

• Rare cases caused by mutations in the presenilin gene

• Later discovered that known a complex in the processing of APP contains a presenilin component

Rare genetic causes may provide clues to understand more common forms of the disease

NIA website
## GENETIC FACTORS

<table>
<thead>
<tr>
<th>PARK Locus</th>
<th>Gene</th>
<th>Map Position</th>
<th>Inheritance</th>
<th>Type of Parkinsonism</th>
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<tbody>
<tr>
<td>Well-validated loci/genes</td>
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<td>AD</td>
<td>EOPD</td>
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<td>Juvenile and EOPD</td>
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<td>1p35–p36</td>
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<td>PARK8</td>
<td>LRRK2</td>
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<td>PARK14</td>
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<td>22q13.1</td>
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<td>Adult onset dystonia-parkinsonism</td>
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<tr>
<td>PARK15</td>
<td>FBXO7</td>
<td>22q12–q13</td>
<td>AR</td>
<td>Early onset parkinsonism-pyramidal syndrome</td>
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</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; EOPD, early onset Parkinson disease; LOPD, late onset Parkinson disease.
PATTERNS OF INHERITANCE: AUTOSOMAL DOMINANT

- Affected Father
  - Non-mutated
  - Mutated

- Unaffected Mother
  - Non-mutated
  - Mutated

- Affected
- Unaffected
PATTERNS OF INHERITANCE: AUTOSOMAL RECESSIVE

Carrier Father                                            Carrier Mother

Non-mutated Mutated

Affected           Carrier                   Carrier            Non-carrier
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<td>LRRK2</td>
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GBA mutations are the most common cause of Parkinsons
ALPHA SYNUCLEIN CAN CAUSE PD

- In 1997, mutations in alpha-synuclein gene identified as a cause of PD
- Duplication and triplication of normal alpha-synuclein cause subtypes of PD
- Common variants around alpha-synuclein gene are associated with lifetime risk of sporadic PD
Intracellular alpha-synuclein is analogous to intracellular tau found in Alzheimer’s disease
ALPHA-SYNUCLEIN TOXICITY

Cookson et al., 2009
LRRK2 MUTATIONS ARE ONE OF THE MOST COMMON GENETIC CAUSES OF PD

- In 2004, mutations in LRRK2 gene discovered to cause PD
- Mutations in LRRK2 account for 2% sporadic PD
- G2019S mutation accounts for over 20% and 40% in Ashkenazi Jewish PD and North African Berbers patients, respectively

Drug companies are interested in targeting the kinase domain of LRRK2 due to the precedent of CML cancer treatment and expertise in developing kinase inhibitors.
LRRK2 INHIBITORS AMELIORATE MUTANT INDUCED CELLULAR DEFECTS

MJFF priority to determine if these class of potential drugs are safe

Sheng et al, 2012
TOXIC INTERACTION BETWEEN MUTANT LRRK2 AND ALPHA-SYNUCLEIN INTERACTION

Ortenstein et al., 2013
WHY DOES THE CAUSE OF PD MATTER?

New disease targets point scientists to where to intervene to stop or prevent the disease.

Strategies from existing clues already in development:

» Targeting alpha-synuclein and LRRK2
» Following epidemiological clues from other studies (e.g., nicotine, caffeine)
» Repurposing drugs approved for other diseases (e.g., isradipine, exenatide)

Strategies to uncover new targets:

» Using advanced genetic sequencing technologies to find new genetic targets
» Exploring pathways known to play a role in Parkinson’s
## THERAPIES IN DEVELOPMENT TO IMPROVE QUALITY OF LIFE

Levodopa Delivery The gold standard for motor symptom treatment brings with it long absorption time, effect maintenance issues (on/off) and side effects (dyskinesia).

- Accordian Pill (Intec)
- ND0611/12 (Neuroderm)

"Off" Rescue When levodopa levels diminish, patients can have a surge of symptoms, called an "off" episode.

- Apomorphine Thin Film (Cynapsus Therapeutics)
- CVT-301 (Civitas)
WHAT WILL HELP US MOVE FASTER?

Biomarkers speed diagnosis and drug development

» Greater understanding of biology
» New drug targets
» Better measurement of disease progression
» Faster testing of disease-modifying therapies
» More detailed patient selection for clinical trials

Researchers have strong leads for Parkinson’s biomarkers and are developing technologies to measure them in risk populations.
HOW WE CAN ALL BE PART OF THE CURE
FOX TRIAL FINDER MATCHES VOLUNTEERS TO THE TRIALS THEY MAY QUALIFY FOR

ABOUT FOX TRIAL FINDER

Fox Trial Finder was created by the Michael J. Fox Foundation to help increase the flow of willing participants — both people with Parkinson’s and control participants who do not have Parkinson’s — into the clinical trials that need them, accelerating the Parkinson’s drug development process.

Clinical trials are a final and crucial step on the path to developing better treatments for Parkinson’s patients today. Around the world, between 40% and 70% of trials face delays because of a lack of volunteers.

Fox Trial Finder will not only list ongoing PD clinical trials and research studies, but will match registrants to the trials that need them and are best-suited to their specific traits. Fox Trial Finder also has a secure and anonymous messaging system, making it much easier to find and act on suitable opportunities to get involved.

JOIN THE 35,892 CLINICAL TRIAL VOLUNTEERS WHO HAVE ALREADY STEPPED UP.

INTERNATIONAL COLLABORATION

The Michael J. Fox Foundation is collaborating with international leaders in PD research to expand Fox Trial Finder in Austria, France, Germany, Italy and Spain.

FROM MICHAEL J. FOX

“The answer is truly in all of us, working together: international collaboration is essential for spreading a cure for the 5 million Parkinson’s patients worldwide.”

— Michael J. Fox

TRIAL TEAMS

Do you need volunteers for your clinical trial? Find them with Fox Trial Finder!

Learn More

Partners in Parkinson’s

A new resource for Parkinson’s patients and caregivers.

Visit www.partnersinparkinsons.org
PARTNERS IN PARKINSON’S: A STRATEGIC HEALTH INITIATIVE

- Seattle: August 16th
- San Francisco: August 9th
- Los Angeles: December 6th
- Denver: November 8th
- Chicago: November 1st
- Cleveland: May 31st
- NYC: May 18th
- Philadelphia: October 18th
- Washington, DC: October 11th
- Atlanta: September 13th
- Boston: September 20th
THANK YOU!

www.michaeljfox.org
www.foxtrialfinder.org
www.partnersinparkinsons.org